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Customer No. 22,852
Attorney Docket No. 03495-0174-01000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Laurent COEN et al.	)	Group Art Unit: 1632
	)	
Application No.: 09/816,467	)	Examiner: S. Chen
	)	
Filed: March 26, 2001	)	
	)	
For: HYBRID PROTEINS THAT MIGRATE RETROGRADELY AND TRANSYNAPTICALLY INTO THE CNS	)	

Mail Stop Appeal Brief--Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANTS' REPLY BRIEF

This is Appellants' Reply Brief in response to the Examiner's Answer, mailed May 18, 2004.

I. Reply to Examiner's Answer

A. The Examiner failed to show that all of the elements of the claimed invention were recited in either Mueller or Höhne-Zell.

The Examiner has failed to demonstrate that all of the elements of the claims are taught by Mueller and Höhne-Zell. Specifically, the use of any portion of tetanus toxin other than fragment C, in addition to fragment C, to obtain a hybrid fragment "capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular

junction and at least one synapse," as required in claims 17 and 18 and the pending claims that depend upon them, is not taught in either Mueller or Höhne-Zell. The element of a hybrid protein comprising fragment B, or a fraction of fragment B having at least 11 amino acid residues, in addition to fragment C, is important in the claimed invention because it provides the advantage of better transport compared with fragment C alone. *See* specification at 7 ("One advantage of the present invention comprising the fragment of tetanus toxin (fragment A, B, and C) is to obtain a better transport of the fragment inside the organism compared with fragment C.").

Thus, without a teaching to include fragment B or a fraction of fragment B having at least 11 amino acid residues, the Examiner has not presented a *prima facie* case of obviousness for claim 17 and the claims that depend on it. Similarly, without a teaching to include fragment B or a fraction of fragment B having at least 11 amino acid residues and a fraction of fragment A devoid of its toxic activity, the Examiner has not presented a *prima facie* case of obviousness for claim 18.

B. Mueller does not teach that the full tetanus toxin protein is a carrier protein.

To argue that the combination of Mueller and Höhne-Zell discloses each element of the claims, the Examiner argued that Mueller *implies* that the full tetanus toxin protein, including fragments A, B, and C can act as a carrier protein. *See* Examiner's Answer at 6. The Examiner further asserted that given the teachings of Höhne-Zell, one of skill in the art would know which regions of fragment A to use in a carrier protein. *See id.* ("Since the toxic activity of tetanus toxin resides at fragment A, in particular amino acids 233 and 234, and Mueller implies the use of the full tetanus toxin that

includes fragments A, B and C, it would have been obvious for one of ordinary skill in the art at the time of the invention to use a tetanus toxin devoid of fragment A or devoid of the active site residues at fragment A of the tetanus toxin protein for neuron specific gene transfer in the central nervous system.").

Applicants disagree that Mueller teaches use of the full tetanus toxin protein as a transport protein, despite the Examiner's characterization of Applicants' argument. *See* Examiner's Answer at 5 ("Applicants argue that Mueller only teaches the neuronal transport property of the full tetanus toxin . . . ."); *cf.* Appeal Brief at 7 ("Mueller investigated whether wheat germ agglutinin or *fragment C* of tetanus toxin could be used to introduce foreign genes into nerve cells. (*See, e.g.,* Abstract on Report Documentation Page.)" (emphasis added)). Mueller observes that it was known by those in the art at the time of the invention that tetanus toxin is capable of retrograde axonal and transynaptic transport to the central nervous system, *see Mueller* at 3-4, an observation that was also made in the specification as background. *See* specification at pages 1-2, 8. That the full tetanus toxin moves retrogradely and transynaptically to the central nervous system does not, though, mean that it can act as a carrier for a heterologous protein fused to it or that it is appropriate as a carrier.

In fact, reliance on Mueller for a teaching to use the *entire* tetanus toxin as a carrier for a fusion protein is flawed because Mueller was aware that there is a toxic region of the protein. If Mueller taught use of the full length protein as an appropriate carrier, the Examiner's argument in support of a motivation to combine Mueller and Höhne-Zell to delete a toxic region would be moot.

Indeed, Mueller does not demonstrate transport of a fusion protein with the entire tetanus toxin, but teaches only transport of the fragment C/horseradish peroxidase fusion protein in Figures 3-5. There is no teaching or suggestion in Mueller to include any part of fragment B, and certainly not "at least 11 amino acid residues" of fragment B, in the fragment C fusion protein, as required in both claims 17 and 18.

Höhne-Zell does not cure this deficiency of Mueller, because Höhne-Zell does not teach anything about fragment B or the requirements of a fusion transport protein. Without a teaching of a fusion protein comprising "fragment B or a fraction of fragment B having at least 11 amino acid residues", the Examiner's statement that

> it would have been obvious for one of ordinary skill in the art at the time of the invention to use a tetanus toxin devoid of fragment A (i.e. comprising fragments C and B) or devoid of the active site residues at fragment A of the tetanus toxin protein (i.e. comprising fragments C and B and the non-toxic part of fragment A) for neuron specific gene transfer in the central nervous system. . . .

Examiner's Answer at 8, is unsupported.

B. The Examiner failed to demonstrate why one of skill in the art would be motivated to combine the teachings of Mueller and Höhne-Zell.

In addition to demonstrating that the combination of the references discloses all of the elements of the claims, a *prima facie* showing of obviousness requires evidence of a motivation to combine. Specifically:

> The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved . . . . Whether the Board relies on an express or an implicit showing it must provide particular findings related thereto. . . . Broad conclusory statements standing alone are not "evidence."

In re Kotzab, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). The Examiner has not provided any specific facts or evidence of a motivation to combine, either from problems in the art or as cited in the references. Instead, the Examiner has vaguely relied on the combination of the references itself as being a motivation to those in the art.

For example, in the Examiner's Answer, the Examiner stated that:

> One of ordinary skill at the time the invention was made would have been motivated to do so in order to generate a non-toxic tetanus fragment capable of retrograde transport as a carrier molecule for neuron specific gene transfer in vivo as taught by Mueller and Hohne-Zell with reasonable expectation of success.

Examiner's Answer at 5. No further information about the need for such a fragment that would provide motivation to combine these two references was provided, though.

The Examiner also attempted to explain the basis for this motivation by asserting that

> the *combination of the teachings of Muller [sic] and Hohne-Zell would motivate* one of ordinary skill in the art to use a tetanus toxin devoid of fragment A (i.e. comprising fragments C and B and the non-toxic part of fragment A) for neuron specific gene transfer in the central nervous system with reasonable expectation of success.

Examiner's Answer at 8 (emphasis added). Similarly, the Examiner argued

> *the teachings of Hohne-Zell and Mueller provide clear and particular evidence that would motivate* one of ordinary skill in the art at the time of the invention to use a tetanus toxin devoid of fragment A of the tetanus toxin protein for neuron specific gene transfer in the central nervous system.

Examiner's Answer at 9 (emphasis added).

These statements, though, indicate that the Examiner has misapplied the requirement of a motivation to combine references when seeking to present a *prima facie* case of obviousness. Specifically, the Examiner has not identified precisely what would motivate one of skill in the art to combine the references, but has only generally referred to the "teachings" of each. The Examiner has asserted that when combined, the references provide motivation, not what would have motivated one to make the combination in the first place. *Cf. McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1352, 60 U.S.P.Q.2d 1001, 1008 (Fed. Cir. 2001) ("the factual inquiry whether to combine references must be thorough and searching.").

C. There would have been no motivation to combine the teachings of Mueller and Höhne-Zell

In fact, there are no factual findings on which the Examiner could rely to support a motivation to combine Mueller and Höhne-Zell. According to the Examiner, Mueller briefly mentions retrograde transport of the entire tetanus toxin and then provides data demonstrating that the tetanus toxin C fragment alone can act as a carrier to direct retrograde transport of an associated fusion protein, such as the horseradish peroxidase enzyme. *See* Mueller at Figs. 3-5. Mueller recites: "C-fragment alone is not toxic, *yet, it is sufficient* for internalization and transport, and therefore could be safely utilized as a carrier molecule for neuron specific gene transfer in vivo." Mueller at 4 (emphasis added). In light of this teaching, there would be no motivation for one of skill in the art to look to Höhne-Zell for an additional fragment.

Furthermore, Mueller produces a preparation of *purified* fragment C for its studies on retrograde transport of the horseradish peroxidase enzyme. The purification step

specifically removes fragment B. *See* Mueller at 4. Given this teaching to exclude fragment B, one of skill in the art would not be motivated to look to Höhne-Zell to include the element of "a fragment B or a fraction of fragment B having at least 11 amino acids residues," as required in independent claims 17 and 18.

Finally, if one wanted to obtain a non-toxic protein, and read Mueller thoroughly, one would be not be guided to add a portion of fragment B to the hybrid protein or to look to articles such as Höhne-Zell that disclose toxic regions of fragment A. Instead of disclosing that fragment A contains the toxic regions of tetanus toxin, Mueller describes fragments B and C as "the cell binding (C-fragment) and *cytotoxic (B-fragment)* portions of tetanus toxin . . . . " Mueller at 4 (emphasis added). Thus, Mueller itself implicates fragment B as toxic, instead of fragment A.

Because neither Mueller nor Höhne-Zell provides any motivation to combine its teachings with the other, and the Examiner has not shown any other factual evidence why one of skill in the art would combine their teachings, a fundamental requirement of *prima facie* obviousness has not been met. *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001) ("In holding an invention obvious in view of a combination of references, there must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention.").

II. Conclusion

The Examiner has failed to support the rejection of claims 17, 18, 21-23, 34, and 35 under 35 U.S.C. § 103 by not demonstrating that each and every element of the

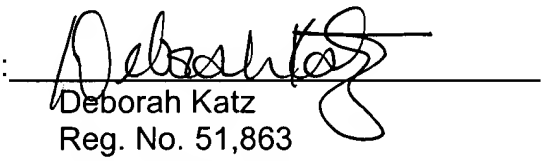
claims is provided in the prior art and by not demonstrating that there was a motivation to combine the references that were cited. Accordingly, the rejection should be reversed.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Reply Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: July 19, 2004

By: 

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